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Effects of a 0.75ppm Sulfur Dioxide on Pulmonary Function Parameters of Normal Human Subjects

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Effects of 0.75ppm Sulfur Dioxide on Pulmonary Function Parameters of Normal Human Subjects

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ABSTRACT. Of 31 young, healthy male volunteers who participated in this study, 15 were exposed to air (control) and 16 to 0.75 ppm (2.15 mg/m^3) SO_2 for 2 hr at 21° C and 60% relative humidity. At the end of the first hour, the subjects exercised for 15 min on a treadmill at 6.4 kmph, with a 10% grade. Methods employed in evaluation of pulmonary function included body plethysmography, spirometry, and multigas rebreathing test. From the battery of 15 pulmonary function parameters, only the pattern of airway resistance changes was significantly altered by SO_2 exposure, although spirometric parameters followed a similar pattern. Eight of the SO_2-exposed subjects, with one or more positive allergen skin tests, appeared to be significantly more reactive to SO_2 than skin test-negative subjects. All subjects remained asymptomatic. The small number of changes observed appeared to be reversible and do not suggest a significant health hazard to normal human subjects exposed to SO_2 under these conditions.

SULFUR DIOXIDE (SO_2) is a common atmospheric pollutant derived primarily from fuel combustion—especially from the burning of coal.[1] Sulfur dioxide is highly soluble in water, and during ordinary nasal breathing there is evidence that most of the inhaled SO_2 is absorbed in the upper airways; only a small amount, if any, penetrates more peripherally where it might be expected to produce an adverse effect.[2]

Exposure of young, healthy subjects to approximately 1 ppm (2.86 mg/m^3) SO_2 for 50 min at rest did not significantly affect pulmonary function.[3] In another study, however, more prolonged exposure (up to 6 hr) to the same SO_2 concentration produced a progressive decrease in FEF_{25-75}.[4] Exercise during exposure seemed to enhance the effects of SO_2, possibly secondary to increased mouth breathing.[5] When young subjects were exposed to 0.37 ppm (1.06 mg/m^3) and 0.75 ppm (2.15 mg/m^3) SO_2 for 2 hr with exercise, no effects were observed at 0.37 ppm level, but a decrease in FEF_{50} was measured at 0.75 ppm.[6] Similar negative findings at 0.4 ppm (1.15 mg/m^3) SO_2 have been reported by other investigators.[7] However, inconsistencies in the results and design shortcomings in the above studies have limited their usefulness in supporting setting of primary and secondary standards. Considerable gaps in the overall SO_2 data base, as well as increasing need of regulatory agencies for relevant data, prompted the authors to extend these observations on the short-term effects of SO_2.

MATERIALS AND METHODS

These experiments were performed in the exposure chambers of the EPA Human Studies Division. The chambers and their physical characteristics have been described in detail elsewhere.[8] The pollutant level maintained in these experiments was 0.75 ± 0.04 [± standard deviation (*SD*)] ppm (2.15 ± 0.11 mg/m^3) SO_2. Relative humidity was maintained at 60%, temperature at 21° C, and light intensity at 50 foot-candles. Recirculation and reconditioning of chamber air through High Efficiency Particle Air (HEPA) filters kept total particle mass at less than 3 μg/m^3, and the particle count at about 1 X 10^5 particles/m^3. Although the level of sulfates was not measured, very low particle count, as well as short residence time, created very unfavorable conditions for the formation of sulfates.

Subjects for this study were healthy, nonsmoking males between the ages of 18 and 40 yr. All subjects were given a comprehensive physical examination, including standard blood laboratory tests. Administration of a Minnesota Multiphasic Personality Inventory Test (MMPI) to each candidate enabled us to reject subjects who might be psychologically affected by experimental conditions. In order to identify potentially hyperreactive subjects, as well as to eliminate asthmatics, each of the subjects had intradermal skin tests consisting of placebo (saline solution), 16 allergen abstracts common to this area (Greer Lab., NC) and 4 methacholine chloride (mecholyl) solutions [0.0625, 0.125, 0.25, 0.5 mg/ml (Table 2)]. The following grading scale was used: 0 = no reaction up to 4-mm wheal; 1+ = 4- to 8-mm wheal; 2+ = 8- to 12-mm wheal; 3+ = >12-mm wheal; and 4+ = >12 mm-wheal, with pseudopod formation. Candidates who had a positive skin response to 7 or more skin allergens and/or showed any reaction to mecholyl were not selected for this study. A total of 31 subjects were studied: 16 were exposed to 0.75 ppm SO_2 and 15 were exposed to air (control). On any given study day, 2 or 3 subjects were exposed. Air and SO_2 exposures were randomly distributed throughout the study period. Subjects entered the chamber at staggered times to allow for the performance of tests in a sequential fashion.

All exposures were for a period of 2 hr. Each subject exercised for 15 min on a treadmill at 6.4 kmph and 10% incline, beginning 45 min after entry into the chamber. Respiratory rate (RR), tidal volume (V_T), minute ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), respiratory quotient (RQ), and heart rate (HR) were measured for 30-sec periods immediately before the exercise and serially at 5 min, 10 min, and 15 min into the exercise period, with HR also monitored for a 3-min recovery following the exercise period. There were four pulmonary function measurement sessions for each subject: 1) baseline, immediately before the exposure (condition #1); 2) at 1-hr of exposure, following a 3-min recovery period from exercise (condition #2); 3) at the end of the 2-hr exposure (condition #3); and 4) 24 hr following the end of exposure (condition #4). Before and after each exposure, a symptom questionnaire was completed by the subject. The following pulmonary function tests were performed.

Plethysmography. A CPI Model 3100 pressure plethysmograph was interfaced to a DEC PDP 11/40 computer for on-line analysis of data. Functional residual capacity (FRC) and airway resistance (RAW) were measured at a panting frequency between 100 and 180 breaths/min. The thoracic gas volume (TGV) and specific airway conductance (SGAW) were also computed.

Spirometry. Forced expiratory measurements were made using a CPI Model 220 rolling seal spirometer interfaced with the DEC PDP 11/40 computer. The output from the spirometer was analyzed on-line[9] and the forced expiratory volume at 1 sec ($FEV_{1.0}$), ratio of $FEV_{1.0}$/FVC, forced expiratory flow at 50% FVC (FEF_{50}), and forced expiratory flow after 75% of FVC exhaled (FEF_{25}) were computed.

Multigas rebreathing test. The technique used in our study was based on the procedure developed by Sackner et al.[10] The analog signals from a Perkin-Elmer MGA-1100 mass spectrometer were converted to a digital form, stored on magnetic tape and later analyzed on a DEC PDP 11/35 computer employing algorithms developed by Friedman et al.[11] The rebreathing measurements included diffusing capacity for CO (D_LCO), pulmonary capillary blood flow ($\dot{Q}_C$), and combined pulmonary tissue and capillary blood volume (VTPC).

To minimize potential sequential interference between tests done during baseline (#1), post-exposure (#3), and 24 hr post-exposure (#4) measurement periods, the tests were administered in the following order: multigas rebreathing performed in triplicate (two best selected for analysis); plethysmography, each maneuver performed satisfactorily twice; and spirometry, each maneuver performed satisfactorily twice. During post-exercise recovery period (#2), only plethysmographic and spirometric measurements were performed as outlined. All data were recorded on magnetic tape for future screening, computerized data validation, and analysis.

For all statistical analyses the mean of the two maneuvers was used. Multivariate analysis of variance was used to test hypothesis H1, that the pattern of change over all four conditions in the SO_2 group was not different from the pattern of change in the air group. If H1 could be rejected, further exploration of the response patterns within the two groups was done by testing additional hypotheses H1A and H1B. H1A was the hypothesis of no difference within the two groups in the change occurring between the baseline measurement and the post-exercise measurement. The H1B was similar to H1A except that the change from baseline to the end-exposure measurement was tested. Since hypothesis H1 was to be tested on the 15 pulmonary function parameters measured in this one experiment, the Bonferroni inequality (see Lee et al.[12]) was used to calculate the *P* value at or below which H1 can be rejected. This procedure ensures an experiment-wise error rate of .05 or less (the level of significance chosen for hypothesis testing in this experiment). The *P* value obtained by this method is .0033 (.5 ÷ 15 = .0033). Actually, the correct *P* value to use for testing H1 for each parameter lies somewhere between .05 and .0033. The .0033 value would apply only if the 15 parameters were totally independent, since the Bonferroni correction is exact in this case. Conversely, the *P* value of .05 would be

acceptable only if the 15 parameters were dependent to the point of being redundant. Since most of the parameters were dependent to some degree, we examined the significance of our results at both P level extremes.

The exercise data were subjected to a simpler analysis, since they did not fit into the multi-condition schedule used with the other data.

RESULTS

Averaged physical characteristics data for the air- and SO_2-exposed groups are shown in Table 1. This Table also shows the mean FVC, $FEV_{1.0}$, and $FEV_{1.0}/FVC$ values expressed in absolute units, and as a percentage of predicted (FVC and $FEV_{1.0}$) values for both cohorts. Between-group comparison of averaged demographic data and pulmonary function indicates that randomized assignment of two relatively small number of subjects produced, in our study, two well-matched groups. The Pearsonian Coefficient of Skewness (PCS), which measures the extent to which a distribution of a sample is skewed, further supports the similarity of the two groups (see Freund[13]). Because for most of the variables the coefficient was between ± 1.0, the skewness was negligible.

The averaged values ± the standard error of the mean (SE) for all 15 parameters are tabulated in Table 3. Comparison of baseline means for both air- and SO_2-exposed groups confirms that pulmonary function of the two groups was well matched. The differences between the SO_2 and air baseline data were negligible and the SEs were quite small. Statistical analysis of these data shows that hypothesis H1 could not be rejected for any of the 15 parameters using a significance level of $P = .0033$. If, however, we use the more liberal P value, i.e., .05 for H1 rejection, then the additional hypotheses, H1A and H1B, can be tested. For RAW, both H1A ($P = .001$) and H1B ($P = .027$) were rejected. Consequently, these results suggest that the differences between the two groups for the change from the pre-exposure to the post-exercise RAW (H1A) and for the change from the pre-exposure and to the end of exposure RAW (H1B) were both significant. In terms of percent differences from the baseline, it can be seen (Table 3 and Fig. 1) that following the exercise period, RAW had decreased 10.3% in the air group, while it had increased 14.6% in the SO_2 group. At the end of the 2-hr exposure, the RAW of the air group had further decreased by 16.7% of baseline, while that of the SO_2 group had returned to the baseline value. The $FEV_{1.0}/FVC$ and FEF_{50} values also showed differences of borderline significance between the response pattern of the air and SO_2 groups ($P = .059$ and .056, respectively). If we reject the H1 hypothesis for these parameters, then both $FEV_{1.0}/$

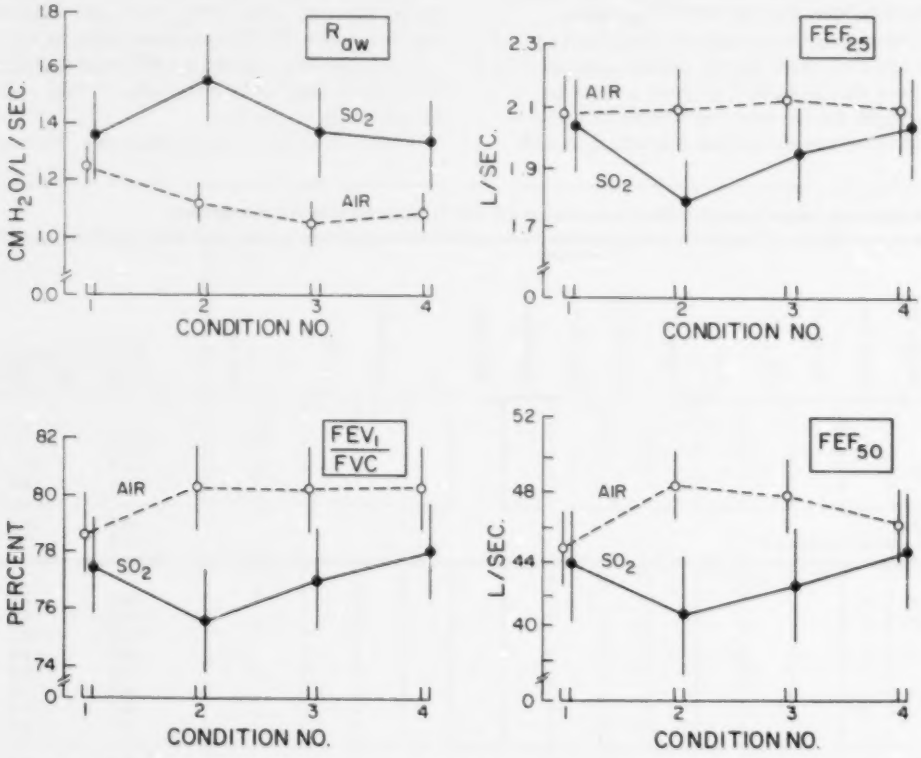

Fig. 1. Mean changes (± 1 SEM) in RAW, $FEV_{1.0}/FEV$, FEF_{25}, and FEF_{50} for 15 subjects in "air" exposure group and 16 SO_2-exposed subjects. Changes were measured: after 1 hr exposure [3 min post-exercise ("condition No. 2")]; at the end of exposure ("condition No. 3") and 24 hr following the end of exposure ("condition No. 4").

Table 1.—Averaged Physical Characteristic Data for Two Groups of Subjects

	Age (yr)	Height (cm)	Weight (kg)	FVC (L)	FVC* (%)	$FEV_{1.0}$ (L)	$FEV_{1.0}$* (%)	$FEV_{1.0}$/FVC (%)
Air-Exposed Group (N = 15)								
Mean	28.5	180.7	73.9	5.36	93.40	4.24	88.60	78.80
SD†	4.89	3.83	7.70	0.49	8.09	0.55	11.10	6.90
Min‡	22.3	173.0	65.5	4.51	78.5	2.72	59.0	79.0
Max§	40.5	186.0	89.4	6.04	103.4	5.11	103.9	85.0
P.C.S.#	1.32	0.52	1.51	−0.24	−0.33	0.16	−0.39	−1.39
SO_2-Exposed Group (N = 16)								
Mean	27.7	180.0	76.1	5.38	95.37	4.19	88.77	77.56
SD	5.35	8.50	8.51	0.82	12.71	0.77	14.45	6.19
Min	24.8	165.0	67.6	4.14	68.9	3.28	63.1	67.0
Max	46.9	191.0	99.6	6.85	125.0	6.03	131.1	89.0
P.C.S.	1.01	−0.35	0.96	0.51	0.22	0.12	0.46	0.03

*Variable expressed as percent of predicted value.[18]
† *SD* = Standard deviation.
‡ Min = Minimum value of the sample.
§ Max = maximum value of the sample.
# P.C.S. = Pearsonian Coefficient of Skewness.

FVC (P = .019) and FEF_{50} (P = .031) will be significantly different, since the H1A hypothesis will also be rejected. The H1B hypothesis, however, could not be rejected for either parameter. The FEF_{25} changes were not significant, although the trend follows that for the FEF_{50} values. Although the subject screening procedure eliminated all those with multiple (i.e., more than 6) positive allergen skin tests, an interaction analysis[13] of the responses to SO_2 of those subjects with at least one positive skin test versus those with none was performed. Individual, as well as averaged values for RAW, $FEV_{1.0}$/FVC, and FEF_{50} (the three most sensitive parameters in this study) indicate that SO_2-exposed, allergen skin test-positive subjects responded to a greater degree than did the skin test-negative subgroup. However, only $FEV_{1.0}$/FVC showed a statistically significant (P = .013) interaction. Subjects with positive skin test response showed a 4.6% mean decrease in $FEV_{1.0}$/FVC, while negative skin test subjects had a mean decrease of only 0.1% (Table 2).

Exposure to SO_2 had no detectable effect on measured

Table 2.—List of Subjects with Positive Intradermal Reaction to Antigens and Their Post-Exercise Lung Function Response

Subject No.	Allergen: Orchard	Red Fescue	Italian Rye	Red Clover	Plantain	Privet	Pigweed	Sh. Ragweed	White Oak	Black Oak	Red Maple	Elm	Red Maple	Hickory	Pecan	Mango	Pulmonary Function* Changes (%): RAW	$FEV_{1.0}$/FVC	FEF_{50}
Air																			
10								+									5.7	1.3	−16.7
27								+									30.5	−1.2	−1.6
32	4+	3+			+				+	+				+			−4.9	21.7	–
36	4+																−33.0	4.9	10.5
Mean (Pos., N = 4)																	−0.4	6.?	−2.6
Mean (Neg., N = 11; all skin tests negative)																	−11.2	0.8	6.5
SO_2																			
4	+	+	+								+			+	+		26.5	−2.4	−1.7
9	4+	3+	+								+			+	+		55.0	−4.8	−25.5
11																+	32.9	−10.1	−33.8
12		+	+				+	+					+				−24.2	−2.8	3.7
22									+		+						17.0	0.0	1.7
25	+	2+												2+	+		6.7	−2.6	−6.8
26	+	+	2+														43.2	−10.4	−22.1
30	2+		+														10.1	−3.8	−1.4
Mean (Pos., N = 8)																	20.9	−4.6	−10.7
Mean (Neg., N = 8; all skin tests negative)																	9.6	0.1	3.5

*Post-exercise to baseline ratio expressed in percent.

Table 3.—Mean Pulmonary Function Changes before, during, after, and 24-hr Post-Exposure to Air (N = 15) and 0.75 ppm SO_2 (N = 16)

Variable		Baseline		Post-Exercise		End-Exposure		24 Hr Post-Exposure		Hypotheses* P Value
		Air	SO_2	Air	SO_2	Air	SO_2	Air	SO_2	
Spirometric values										
FVC	Mean	5.36	5.38	5.39	5.40	5.35	5.37	5.37	5.35	H1: 0.880
(L-BTPS)	SE	0.13	0.21	0.14	0.20	0.14	0.19	0.14	0.19	
	Diff. (%)	–	–	0.6	0.4	−0.2	−0.2	0.2	−0.6	
$FEV_{1.0}$	Mean	4.24	4.19	4.35	4.10	4.29	4.16	4.33	4.20	H1: 0.119
(L-BTPS)	SE	0.14	0.19	0.12	0.16	0.13	0.17	0.12	0.18	
	Diff. (%)	–	–	2.6	−2.1	1.2	−0.7	2.1	0.2	
$FEV_{1.0}$/FVC	Mean	78.8	77.6	80.4	75.7	80.3	77.2	80.4	78.2	H1: 0.059
(%)	SE	1.8	1.5	1.5	1.6	1.5	1.6	1.5	1.7	H1A: 0.019
	Diff. (%)	–	–	2.0	−2.4	1.9	−0.5	2.0	0.8	H1B: 0.234
FEF_{50}	Mean	4.45	4.34	4.82	4.05	4.74	4.23	4.57	4.43	H1: 0.056
(L/sec)	SE	0.26	0.35	0.24	0.23	0.30	0.29	0.22	0.33	H1A: 0.031
	Diff. (%)	–	–	8.3	−6.7	6.5	−2.5	2.7	2.1	H1B: 0.036
FEF_{25}	Mean	2.08	2.04	2.10	1.79	2.14	1.96	2.11	2.05	H1: 0.107
(L/sec)	SE	0.15	0.18	0.16	0.16	0.16	0.18	0.17	0.19	
	Diff. (%)	–	–	1.0	−12.3	2.9	−3.9	1.4	0.5	
Plethysmographic values										
FRC	Mean	3.77	3.61	3.76	3.71	3.67	3.63	3.68	3.55	H1: 0.624
(L-BTPS)	SE	0.18	0.23	0.13	0.20	0.17	0.23	0.17	0.24	
	Diff. (%)	–	–	−0.3	2.8	−2.7	0.6	−2.4	−1.7	
RAW	Mean	1.26	1.37	1.13	1.57	1.05	1.37	1.09	1.33	H1: 0.011
(cm H_2O/L · sec)	SE	0.09	0.12	0.06	0.15	0.06	0.17	0.07	0.16	H1A: 0.001
	Diff. (%)	–	–	−10.3	14.6	−16.7	0.0	−13.5	−2.9	H1B: 0.027
TGV	Mean	4.14	4.22	4.28	4.31	4.24	4.19	4.13	4.10	H1: 0.833
(L-BTPS)	SE	0.15	0.22	0.18	0.23	0.18	0.23	0.18	0.24	*
	Diff. (%)	–	–	3.4	2.1	2.4	−0.7	−0.2	−2.8	
SGAW	Mean	0.20	0.18	0.21	0.16	0.23	0.20	0.24	0.21	H1: 0.132
(L/sec · cm H_2O)	SE	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.01	
	Diff. (%)	–	–	5.0	−11.1	15.0	11.1	20.0	16.7	
Ventilatory values										
V_T	Mean	1.25	1.23	1.18	1.20	1.29	1.25	1.25	1.16	H1: 0.279
(L-BTPS)	SE	0.09	0.09	0.08	0.09	0.10	0.10	0.10	0.08	
	Diff. (%)	–	–	−5.6	−2.4	3.2	1.6	0.0	−5.8	
f_b	Mean	18.4	19.2	19.1	17.5	18.6	19.6	20.0	20.1	H1: 0.231
(bpm)	SE	1.2	1.3	1.5	1.1	1.4	1.0	1.1	1.1	
	Diff. (%)	–	–	3.8	−8.9	1.1	2.1	8.7	4.7	
$\dot{V}_E$	Mean	22.1	22.6	21.8	20.3	23.2	23.9	22.9	24.8	
(L/min)	SE	1.1	1.7	1.8	1.4	2.0	2.2	2.0	2.2	
	Diff. (%)	–	–	−1.4	−10.2	5.0	5.7	3.6	9.7	
Multigas rebreathing values										
$D_{L_{CO}}$	Mean	22.2	23.7	–	–	20.2	25.5	20.4	24.4	H1: 0.167
(ml/mm Hg X min)	SE	2.0	0.5	–	–	1.5	2.1	1.8	0.9	
	Diff. (%)	–	–	–	–	−9.0	7.6	−8.1	4.6	
VTPC	Mean	481.0	488.0	–	–	505.0	536.0	485.0	500.0	
(ml)	SE	65.0	65.0	–	–	40.0	53.0	37.0	25.0	
	Diff. (%)	–	–	–	–	5.0	9.8	0.8	2.5	
$\dot{Q}_C$	Mean	5.3	4.8	–	–	4.8	4.8	5.4	5.6	
(L/min)	SE	0.6	0.2	–	–	0.3	0.4	0.5	0.3	
	Diff. (%)	–	–	–	–	−9.4	0.0	1.9	16.7	

NOTE: All abbreviations are defined in text.

*Degrees of freedom for H1 are 3,27; for H1A and H1B are 1,29.

†Air group, N = 6; SO_2 group, N = 6.

physiological response to exercise, i.e., RR, V_E, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, RQ, and HR. During exercise, $\dot{V}_E$ increased to about 60 L/min, $\dot{V}_{O_2}$ to about 2.5 L/min, and HR from a resting mean of about 71/min to approximately 140/min. After 3 min of recovery, HR in the air group dropped to about 83 beats/min, while in the SO_2 group HR dropped to about 90 beats/min. None of the slight differences between the groups were statistically significant.

None of the parameters linked to pulmonary hemodynamics (multigas rebreathing test) was significantly changed by air or SO_2 exposures (Table 3).

The symptom questionnaire revealed no consistent responses or complaints of undue discomfort or stress related to exercise in either the air or SO_2 groups.

DISCUSSION

In this study, only those measures related to air flow resistance were significantly affected by SO_2 exposure. In 14 of the 16 SO_2-exposed subjects, RAW was increased between 2% and 55% at the end of the first hour of exposure, with a mean increase of 14.6%. This contrasts with a 10.3% decrease in mean RAW in the control group. Most of the other parameters exhibited a similar post-exercise pattern of response, i.e., decrease in the SO_2-exposed group and slight improvement in the air group.

Since the exercise level and associated physiologic responses were essentially the same in both groups, the decrements in lung function observed in the exposed group apparently reflect SO_2-induced bronchoconstriction which prevailed over exercise-induced bronchial relaxation. Even at the conclusion of the exercise period, the mean SO_2-induced changes observed were small in magnitude, unassociated with symptoms, and presumably of no clinical significance.

When considered individually, some subjects had a more pronounced decrement in lung function at the conclusion of the exercise period, but recovered during the second hour of exposure. This adverse effect of exercise in an SO_2-containing atmosphere is consistent with the results reported by Frank et al.[14] The underlying mechanism of the exercise effect may be related to increased peripheral penetration of SO_2 possibly due to increased inspiratory air flow and/or increased mouth breathing. Both factors would result in reduced absorption of SO_2 in the upper airways by bypassing the nasopharyngeal passages and by reducing the time for solution of SO_2 in the mucosal layer lining the upper airways.[2] Indeed, Snell and Luchsinger[15] reported that mouth inhalation of 0.5 ppm SO_2 for 15 min decreased FEF_{50}. This decrement became even greater (and statistically significant) when the SO_2 concentration was increased to 1.0 ppm.

Although increased ventilation appears to be an important determinant of the degree of SO_2-induced lung function alteration, the concentration of inhaled SO_2 is equally important. Bates and Hazucha[6] showed that although a 1-hr exposure of 4 normal subjects to 0.75 ppm SO_2 with two 15-min exercise periods decreased FVC, $FEV_{1.0}$, and FEF_{50} by 6.4%, 5.1%, and 15.7%, respectively, lowering of the SO_2 concentration while maintaining the exercise load failed to affect pulmonary function. Bedi et al.[7] were not able to demonstrate spirometric effects of exposure to 0.4 ppm SO_2 with four 15-min exercise periods during the 2-hr exposure.

Although precise comparisons with the data of Bates and Hazucha[6] and Bedi et al.[7] are difficult to make because of differences in exercise regimen or SO_2 level, the spirometric changes observed in our study are compatible with those reported by those investigators.

From these observations, it appears that SO_2 will elicit a measurable airways response in healthy subjects only when a certain rate of SO_2 loading is exceeded. Below this critical load, the respiratory system is apparently capable of neutralizing SO_2 and its metabolites rapidly enough that no immediate respiratory mechanics effects can be discerned.

Although the data provided by our experiments give no information on the mechanisms of SO_2 action, the elevated RAW and trend toward decreased FEF_{50} and $FEV_{1.0}$/FVC implicate bronchoconstriction. In normal individuals, SO_2-induced bronchoconstriction appears to be mediated primarily by a vagal reflex.[16] In hyperreactive individuals, however, non-vagal (immunological) mechanisms may also be important.[17] It is in this context that our findings regarding skin test-positive subjects may be of importance. This subgroup appeared to be more responsive to SO_2 than the skin test-negative subgroup. It would, therefore, appear useful to have further studies performed on atopic subjects with and without asthma in order to make a more comprehensive assessment of the effects of SO_2 on important segments of the population.

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